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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
01/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,521	SCHREIBER, GIDEON	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,66-71,75-82 and 87-93* is/are pending in the application.

4a) Of the above claim(s) *87 and 90-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,66-71,75-82,88,89 and 93* is/are rejected.

7)☒ Claim(s) *88 and 89* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicant's response of October 18, 2007, to the non-final action dated July 2, 2007 has been entered. Claims 62, 66-71, 75-82 and 87-93 are pending in the application. Claim 88 has been amended and claim 94 cancelled. No claims were newly added. Claims 87 and 90-92 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 62, 66-71, 75-82, 88, 89 and 93 are under current examination.

Response to Claim Objections

Claims 88 and 89 stand objected to as encompassing non-elected subject matter. Applicants' disagree, arguing that the claims shall be restricted if no generic claim is finally held to be held allowable. As no allowable subject has been indicated, the claim objections are maintained.

Response to Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 62, 66-71, 75-82 and 93 stand rejected under 35 U.S.C. §112, first paragraph, for lacking an enablement for the full scope of the invention. The rejection set forth on pp. 6-7 of the office action dated July 26, 2006, and pp. 3-5 of the office action dated July 2, 2007 is maintained, for reasons of record.

Applicants disagree with the rejection and state that claim 62 and dependent claims 66-71, 75-82 and 93 each contain limitations that require: (1) that the polypeptide comprises the sequence of SEQ ID NO:2; (2) that the polypeptide contains alanine substitutions at positions 78 and 100 of the extracellular domain; and (3) that said substitutions synergistically increase the affinity of the claimed polypeptide for IFN-βcompared to the wild type polypeptide. Accordingly, the scope of the claim does not extend to polypeptides which do not retain the

synergistic increase in affinity for IFN-β. and do not encompass the "change, deletion, or addition" of "any of numerous amino acids to various regions of SEQ ID NO: 2 that can introduce substantial variation, affecting binding of IFN-β." Applicants additionally argue that Bowie is entirely irrelevant as Bowie is directed to the determination of a protein's function from its structure which clearly has no place in an enablement analysis wherein the function of the claimed polypeptide is known, as is the case here. Further arguing that fusion proteins comprising SEQ ID NO:2 with the claimed alanine substitutions, such fusion proteins can be created without undue experimentation by one of ordinary skill in the art and would not be expected to interfere with the synergistically increased affinity for IFN-β relative to the wild type protein. Applicant's arguments have been fully considered, but are not found persuasive.

As previously indicated, page 1, paragrpah [0003] of the the amended specification states: type I interferons include interferon α, interferon β and interferon ω, while type II interferon includes interferon γ. IFNAR 2 is the beta subunit or beta chain of the type I IFN receptors (p. 2, paragraph [0006], and as the polypeptide claimed in claim 62 comprises the sequence of SEQ ID NO: 2, other type I IFN receptors cannot be excluded, and hence the claims encompass polypeptide sequences of numerous receptor variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms. Therefore, while the enabled scope of may not extend to polypeptides which do not retain the synergistic increase in affinity for IFN-β, the claimed scope clearly does, and thus highlights the enablement issue. As previously stated, the enabled scope of the claims is limited to an isolated human IFNAR2- EC polypeptide, wherein amino acid residues His 78 and Asp 100 of the extracellular domain are substituted by alanine, as set forth in SEQ ID NO: 2.

In response to Applicants' assertion that Bowie is entirely irrelevant as Bowie is directed to the determination of a protein's function from its structure which clearly has no place in an enablement analysis wherein the function of the claimed polypeptide is known, it should be noted that what is known regarding function is the IFNAR2- EC polypeptide, and its mutant, as set forth in SEQ ID NO: 2. What is not known with regard to function are the numerous variants encompassed by the instant claims. As previously stated: Bowie, et al. (Science, 247: 1306-10, 1990; or record) provide notable insight into the lack of reasonable predictability for the

mutation of any particular protein. Bowie state that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). Bowie continues: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10). Therefore, it remains unknown whether the mutations of his 78 and asp 100 in SEQ ID NO: 2 would retain their synergistic increase in binding IFNβ, following a fusion to any of numerous unknown amino acid sequences of unlimited size, that can introduce substantial variation, affecting binding of IFNβ. It is apparent therefore that Bowie et al. is highly relevant to the non-enabled embodiments encompassed by the instant claims.

Thus, the rejection of claims 62, 66-71, 75-82 and 93 is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 112-Lack of Enablement

Claims 88, 89 and 94 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant's cancellation of claim 94 renders its rejection moot. The rejection set forth on pp. 5-7 of the office action dated July 2, 2007 is maintained, for reasons of record.

Applicants traverse the rejection, arguing that the claims are directed to the use of a composition comprising the polypeptide of claim 62 to augment the anti-cancer, immune modulating or antiviral properties of IFNβ, and that the full scope of each claim is enabled in view of the present disclosure and the knowledge available to one of ordinary skill in the art at the time of the instant application. Applicants state that Examples 4 and 7 and Figure 4, provides a working example demonstrating enhanced activity of IFN-β/IFNAR2 (wild type and mutant) complexes relative to free IFN-β, and the addition of IFNAR2 to a constant amount of IFN-β

resulted in a dose-dependent increase in cell survival upon challenge with vesicular stomatitis virus (VSV). Further arguing that these results are applicable to any therapeutic indication in which free IFN-β has shown therapeutic activity, including the claimed anti-cancer and immune modulatory activities.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicants should note that the examination of the instant claims has been limited to the scope of the elected species of "anti-viral properties" and "multiple sclerosis". Regarding Figure 4, the figure merely depicts binding curves for IFN-β and IFNAR2 wild type and mutant forms and is used to extrapolate the amount of free IFN-β in the anti-viral assay. The anti-viral assay described in Example 7 is an *in vitro* assay on human amniotic cells and does not provide any information regarding dose dependent increase in cell survival, and more importantly, provides no information with regard to immune modulatory activity. Moreover, the prior art of Hertzog et al. (of record) describe a method of regulating interferon type I functional activity by administering a soluble IFNAR2a soluble receptor (p.1, paragraph 1). Herzog also showed that soluble IFNAR2a has been found to inhibit the functional activity of type I interferon, i.e. IFN-β (p.3, first paragraph). Thus, the IFNAR2's function as a carrier of IFN-β would appear to be antagonistic to the anti-viral activity of IFN-β . Thus, the guidance provided by the instant specification is insufficient in teaching a person of ordinary skill in the art to augment IFN-β activity in autoimmune disease and multiple sclerosis. The specification is silent on the claimed composition having been administered to a patient having an autoimmune disorder or multiple sclerosis, either alone or in combination with IFN.

Applicants' arguments with reference to European Patent No. EP 1037658 B (WO 99/32141) and the titration of the mutant receptor at varying concentrations to a given concentration of IFN-β, resulting in a switch from protagonist to antagonist are found persuasive. However, issues regarding determining whether the binding of any of numerous unknown and yet to be discovered receptor molecules that additionally exhibit a therapeutic effect in treating autoimmune disease, including multiple sclerosis remain to be addressed.

Thus, the rejection of claims 88 and 89 is maintained for reasons of record and the discussion set forth above.

Response to Claim Rejections - 35 USC § 103

Claims 62, 66-71 and 75-76 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. (of record). The rejection set forth on pp. 8-9 of the office action dated July 26, 2006, the Advisory action dated October 17, 2006, and pp. 7-9 of the office action dated July 2, 2007 is maintained for reasons of record.

Applicants traverse the rejection, arguing that the Examiner cited Piehler et al. out of context, because while Piehler et al. describe the mutant H78A as stabilizing the complex with IFN-β nearly two fold; the mutation N100A decreasing dissociation rate constant for IFNβ by almost fourfold; state: "It would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2, which should have about a 20-fold tighter binding for IFNβ compared to IFNα2." Concluding that Piehler et al. does not demonstrate any expectation of synergism, and it is the synergism of the claimed polypeptide for IFN-β compared to the wild type polypeptide that must be considered. Applicants further argue that the instant specification, at page 23, paragraph [0093], teaches that "the affinity of the IFNAR2 [H78A/N100A] mutant was found to be approximately 100 times higher than the wild type towards IFN-β and unchanged towards IFNα2", thus providing further evidence of nonobviousness.

Applicant's arguments have been fully considered, but are not found persuasive. Piehler et al. specifically state that it would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2. If the outcome of the double mutation could be accurately predicted, it would not be "interesting" to explore such a result. When the teachings of Piehler are considered in total, there is no basis for predicting an absence of synergy between the two mutations in increasing the affinity of the ifnar2 receptor for IFN-β. Further, to the extent that they are enabled, the instant claims are directed to a product, that is an isolated human IFNAR2- EC polypeptide, wherein amino acid residues His 78 and Asp 100 of the extracellular domain are substituted by alanine. Therefore, the claimed product is specifically described by Piehler et al. Hence, the product must necessarily possess an increased affinity for IFN-β, as Piehler et al. showed increased affinities (of twofold and fourfold respectively) for each of the separate mutations, with the N100A mutation hardly affecting the rate of IFNα2 binding. Piehler et al.

further predicted a 20-fold tighter binding for IFNβ compared to IFNα2, in the IFNAR2 receptor harboring both mutations. Piehler et al. state that IFNα2 and IFN-β bind competitively to the same functional epitope (second column, p. 234), and that the N100A mutation hardly affects the binding of IFNα2, and the H78A destabilized the complex with IFNα2 only twofold (first column, p. 230); additionally stating: "Two mutations on ifnar2 (H78 and N100) result in an increased rate of dissociation (and thus higher affinity) for IFNβ but not for IFNα2." (first column, p. 234). Thus, that the two mutations synergistically increased binding affinity for IFN-β is not considered an unexpected result. The mutations and resulting higher affinities for IFN-β are in relation to the wild type un-mutated polypeptide.

Therefore, the rejection is maintained for reasons of record and the foregoing discussion.

Claims 77-82 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. (of record), in view of Campbell et al. (of record). The rejection set forth on pp. 8-9 of the office action dated July 26, 2006 and p. 9 of the office action dated July 2, 2007 is maintained, for reasons of record.

Applicant disagrees with the rejection, citing the deficiency of Piehler et al. in teaching the synergistic effect of the H78A/N100A double mutant, and Campbell does nothing to remedy the defect of Piehler. Such is not found persuasive, in view of the discussion set forth above. Therefore, the rejection is maintained for reasons of record and the foregoing commentary.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 6:30 AM-3:30 PM EST pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

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